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RECENT WORK DONE AT THE LABORATORY OF GENERAL AND COMPARATIVE PHYSIOLOGY, INSTITUTE OF ANIMAL MORPHOLOGY IMENI A. N. SEVERTSOV, ACADEMY OF SCIENCES USSR

[Comment: The following report is a complete index and review of papers published in Trudy Inst Morfol Zhivotnykh imeni A. N. Severtsova, Issue 6, 1952.]

Introduction by Kh. S. Koshtoyants, Head of the Laboratory of General and Comparative Physiology, Inst of Animal Morphology imeni A. N. Severtsov, Academy of Sciences USSR, pp 3-4.

The work described in this collection of papers is subdivided according to two broad classifications, enzyme-chemical relationships existing in the nerve systems of various animals, and results of comparative investigation of the respiratory function of blood. These two lines of research have been pursued at the Laboratory of General and Comparative Physiology during a number of years, and the results of the work in question have been embodied in special communications, monographs, and candidates' and doctors' dissertations.

In a number of articles published in the first division of this collection, results are summarized which have led to conclusions that there is a profound connection between proteins, metabolism, and nerve regulation from the standpoint of general problems of the evolution of functions of the nerve system as well as of the trophic effects exerted by this system. The articles in question show the significance of functional groups of proteins (particularly sulphydryl groups) as the basis of the excitation of protein. They also demonstrate the role of these groups in the stimulation of living matter, i. e., in the end effect produced by the action of various nerves. New factual data on the distribution in the nerves of various animals of so-called chemical transmitters are cited. These transmitters were investigated in the same system with enzymes which participate in their formation and destruction as well as in their mutual interaction. It was shown that this system is both an end result and a link in the general sequence of metabolic processes. This sequence is effective by reason of enzyme-chemical connections with the principal stages of processes on which the functional activity of the organs activated by the nerves is based.

- 1 -

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The articles in question tend to clarify in part the enzyme-chemical foundations of the nerve process. They both develop and confirm I. P. Pavlov's teaching on the trophic effects of the nervous system.

The new data and conclusions were obtained in the laboratory not only on the basis of an experimental and comparative physiological analysis, but also as a result of dealing with practical problems pertaining to the nature of pain and the action of analgesics, ways in which the chemical dynamics of the nervous system are interfered with in traumatic injuries, and the role of narcosis in such conditions.

The articles in the second part of the book deal with the results of a comparative experimental investigation of the respiratory function performed by the blood of various animals.

1. Investigations of the Enzyme-Chemical Nature of Nerve Activity.

"Proteins, Metabolism, and Regulation by Nerves," Kh. S. Koshtoyants, pp 7-18

Living matter was capable of receiving stimuli and of being excited by these stimuli at a stage of evolution which preceded the development of nerves. The sensitivity which living matter (i.e. protoplasm) exhibits without participation of nerves is due to the reactivity of proteins. From this point of view, the role played by the so-called functional proteins (myosin) is of particular importance. In the reversible changes of functional proteins, the sulfhydryl group is especially significant. Cadmium chloride, by reacting with sulfhydryl groups, stops the beating of a frog's heart. The function of the heart is restored by an extremely small quantity of cysteine. In the course of our work, we set ourselves the task not only of introducing from the outside substances which contain sulfhydryl groups, but also of liberating reserve sulfhydryl groups already present in proteins by exposing these proteins to the action of such substances as urea or guanidine. Sulfhydryl groups and the poisons acting on them are also of importance in the coagulation of blood.

It has been shown that galvanotaxis of parameria is dependent on sulfhydryl groups and that inhibition of the activity of these groups by thiol poisons (HgCl₂) stops galvanotaxis (M. F. Popova, 1952). Addition of substances containing free sulfhydryl groups restores the lost capacity.

Our experiments (Kh. S. Koshtoyants and T. M. Turpayev, DAN SSSR, Vol LIV, No 2, p 181, 1946) demonstrated that suppression of heart activity under the influence of the vagus or under the equivalent effect of acetylcholine is prevented when the sulfhydryl groups are chemically blocked. The effect is restored by the addition of cysteine, but not by the addition of cystine. A subsequent investigation (Kh. S. Koshtoyants and K. S. Logunova, DAN SSSR, Vol LXXIII No 2, 429, 1950) showed that the phenomenon of the "escape" of the heart from the depressing action of the vagus, which is well known to physiologists, must be ascribed to the dearth of available sulfhydryl groups. If more sulfhydryl groups are made available with the aid of urea, the reactivity which brings about depression is restored.

Analogous conditions were found to exist as far as the regulation of skeletal musculature is concerned (Kh. S. Koshtoyants, DAN SSSR, Vol LXXII, No 5, p 981, 1950). Further experiments showed that the elimination of fatigue in tired muscles depends on sulfhydryl groups and that the action of motor and vegetative nerves of the frog also depends of the state of the sulfhydryl groups of proteins.

- 2 -

S-E-C-R-E-T

S-E-C-R-E-T

50X1-HUM

One may assume that further experimental work will clarify the significance of other reactive groups of proteins besides sulfhydryl in processes of physiological regulation. This is suggested by A. M. Budanova's experiments (DAN SSSR, Vol LXXV, No 6, p 875, 1950), who showed that an epileptogenic zone of the brain cortex (a zone which was produced by refrigerating a section of the cortex) has an increased content of free ammonia, and that introduction into the blood of glutamic acid, which participates in the binding of ammonia through the biological synthesis of amide, alleviates epileptic seizures. The intimate connection between the nervous system and proteins is also indicated by N. N. Demin's experiments (DAN SSSR, Vol LXII, No 1, p 145, 1948; 1952), which demonstrated the effect of acetylcholine on the structure of proteins and on the course of a number enzymatic processes, first of all autolysis. The results of my experiments (DAN SSSR, Vol LX, No 6, p 1105, 1948) clearly showed that excitation of a nerve (irritation of the vagus) is accompanied by activation of hyaluronidase. In this connection, one may note that histamine and acetylcholine, which are known to participate in processes of nerve excitation, exert an activating effect on the enzyme hyaluronidase (D. Ye. Ryvkina, Biokhimiya, Vol XVII, No 1, p 25, 1952).

The sensitivity of nerve receptors to various physiological stimuli is influenced by the condition of the sulfhydryl groups, as experiments performed by me together with S. A. Mirzoyan and S. G. Dovlatyan prove. Using the method of ear perfusion, we established that acetylcholine which has been introduced into the ear of a rabbit connected to the head only by its nerves, produces a drop of blood pressure through reflex action. However, if the sensorivascular elements of the rabbit ear are subjected to the action of cadmium chloride, which binds sulfhydryl groups, the clear effect of a reflexory drop of blood pressure in response to the action of acetylcholine on the vascular receptors disappears. The sensitivity of these receptors can be fully restored by perfusing the blood vessels of the ear with cysteine or urea.

It was shown in experiments performed at our laboratory that hydrochloric acid which has been introduced into the intestine stimulates pancreatic secretion by acting on the nervous system. Data obtained by Ts. V. Serbenyuk (DAN SSSR, Vol LXXV, No 1, p 145, 1950) indicate that after the vagus, which is the secretory nerve of the pancreas, has been inactivated by means of atropine, the elimination of pancreatic juice in response to the action of hydrochloric acid is reduced by 50%. In addition to that, the activity of pancreatic enzymes (trypsin, lipase, and amylase) is sharply reduced. In further experiments carried out under participation of Serbenyuk and G. D. Tur'yeva, we established (by observing the effects of cadmium chloride and of cysteine applied to the intestine) that the action of hydrochloric acid which has been described above depends on the availability of free sulfhydryl groups in the receptors of the intestine. Experiments performed by me together with T. G. Putintsova on frogs showed that thiol poisons (cadmium chloride) interfere with the reflex activity of the spine down to complete disappearance of reflexive responses of muscles of the legs to irritation by acid. The introduction of cysteine restored the reflexes.

The connections between nerve regulation on the one hand, and the structure of proteins and metabolism on the other, are apparent from many experimental results. These includes data obtained by T. A. Speranskaya in the work cited below as well as our results on the changes in the molecular structure of glycogen produced by nerve atrophy (Kh. S. Koshtoyants, Z. Yanson, DAN SSSR, Vol LXXV, No 6, p 881, 1950).

"The Role of Sulfhydryl Groups of Tissues in Bringing About the Action of the Vagus on the Heart," T. M. Tupayev, pp 19-37

- 3 -

S-E-C-R-E-T

S-E-C-R-E-T

50X1-HUM

The normal sensitivity of the frog myocardium to acetylcholine and impulses transmitted by the vagus may be disturbed by the action of various agents which modify the metabolism of the heart muscle. Such substances are mercuric chloride in concentration 5×10^{-5} ; 1×10^{-4} and hydroxyphenylarsineoxide in the concentration 1×10^{-4} . In the concentrations indicated, these substances do not interfere with the contractile capacity of the heart muscle when applied for 30-60 sec. Substances that contain free sulfhydryl groups (cysteine, 2,3-dimercaptopropanol) restore the action of the vagus and of acetylcholine on the myocardium after this action has been lost due to the effect of thiol poisons. This indicates that sulfhydryl groups play an important role in bringing about the action of acetylcholine on the myocardium. The action of acetylcholine on the myocardium may also be eliminated by means of the enzyme poison sodium fluoride.

The contraction of the heart muscle of the frog is also strongly dependent on the presence of free sulfhydryl groups. Binding of the latter by thiol poisons (alloxan, aminophenophenylchloroarsine hydrochloride, and salts of mercury, silver, copper, and cadmium) deprives the muscle of contractile properties. Subsequent introduction of cysteine or 2,3-dimercaptopropanol restores the contractile properties of the myocardium. After the sulfhydryl groups have reacted with a thiol poison, adenosinetriphosphate does not exert its usual stimulating effect on the myocardium. The assumption is that thiol poisons suppress the contractile properties of the heart muscle by interfering with its energy-supplying metabolism.

It was established that a competitive relationship between acetylcholine and thiol poisons exists at concentrations which suppress contraction. Against the background of suppression by acetylcholine, thiol poisons exert a much weaker effect on the strength of contractions of the myocardium than would be the case without prior introduction of acetylcholine.

The action of acetylcholine on the myocardium results from the effect which this substance exerts on the metabolic processes of the effector tissue. This illustrates the enzyme-chemical nature of the action exerted by the vagus on the heart.

"Ammonia and Glutamine in the Cerebrum and Nerves of Warm-Blooded Animals Subsequently to Electrical Irritation," A. M. Budanova, pp 38-42

The results of the experiments described show that the contents of both ammonia and glutamine increase in the brain of rabbits after electrical irritation. In the brain of rats, the amount of ammonia increases under similar conditions, while that of glutamine decreases. In the case of guinea pigs, the content of both chemicals decreases in the brain subsequently to electrical irritation. In the sciatic nerve of rabbits, the content of both substances remains unchanged after the nerve has been irritated by an electrical discharge. These data prove that glutamine is not only produced by the detoxification of ammonia by means of glutamic acid, but also plays some additional biological role which varies with the stage of ontogenesis.

"The Effect of the Nerve System on the Structural State of Muscle Proteins," T. A. Speranskaya, pp 43-52

In the process of recovery after a reversible injury inflicted by means of ethyl ether, skeletal muscles with preserved nerve connections recover 30% faster than muscles with severed nerves. This was established by the method of dyestuff absorption. The conditions brought about by denervation do not increase the susceptibility of the muscle to injury during the time of the experiment. The influence of the nerve does not prevent injury: it only

- 4 -

S-E-C-R-E-T

S-E-C-R-E-T

50X1-HUM

expedites recovery. The restorative effect of the nerve system is due to direct participation in the metabolism of the innervated tissue: no vascular effects are involved. This could be shown by tying off the blood supply. The trophic effect of the nerve system extends to profound changes in the physicochemical structure of living tissue and contributes to the reversibility of changes occurring in proteins of damaged muscles.

"The System Histidinedecarboxylase - Histamine - Histaminase Under Various Functional Conditions of the Nerves," D. Ye. Ryvkina, pp 53-92

Histamine was present in all nerves investigated by us regardless of their physiological characteristics (i.e. whether afferent or efferent, somatic, sympathetic or parasympathetic vegetative). As a result of threshold irritations, the content of histamine in nerves increases; after strong irritation it decreases and occasionally disappears altogether. Upon irritation of isolated nerves, the excretion of histamine by them into the surrounding liquid increases. Narcosis augments the stability of histamine in nerve tissue. Nerve tissue contains the enzymes histidinedecarboxylase and histaminase. The quantity of acetylcholine in nerves changes parallel to variations in the quantity of histamine which is present in them. On irritation of cholinergic nerves, the content of histamine in the innervated tissue changes. Conduction in afferent nerves and the sensation of pain have a twofold chemical basis: they depend on both histamine and acetylcholine.

"Relationships Between the Content of Acetylcholine and Histamine and the Activity of Enzymes Which Destroy them in the Nerves of Various Animals. Communication No 1: The Content of Acetylcholine and Histamine in the Nerves of Invertebrates, Fishes, and Amphibia," R. L. Mitropolitanskaya, pp 93-97

Considerable differences in the histamine content in various branches of the vagus of the same animal were established.

"Relationships Between the Content of Acetylcholine and Histamine and the Activity of Enzymes Which Destroy them in the Nerves of Various Animals. Communication No 2: Histaminase and Cholinesterase in Various Nerves of Fishes and Amphibia," R. L. Mitropolitanskaya, pp 98-102

"The Interrelationship Between Acetylcholine and Histamine in Connection with the Problem of the Enzyme-Chemical Nature of Nerve Stimulation," T. G. Putintseva, pp 103-114

Acetylcholine exerts an antihistaminic effect on the smooth musculature of the small intestine of guinea pigs and susliks (*Citellus citellus*) as well as on the lungs and bladder of frogs. Prior treatment of the specimen with histamine has no effect on acetylcholine contraction. Prolonged cooling (in excess of 2 hrs) of frog lungs at plus 10° leads to suppression of sensitivity to histamine. Acetylcholine under these conditions still produces contraction. A section of the small intestine of a hibernating animal like the suslik does not respond by contraction to the action of histamine at plus 50°. When the temperature is raised to plus 37°, the reaction to histamine is restored. The action of acetylcholine on a specimen of this tissue changes only quantitatively with temperature, not qualitatively. Keeping a section of the small intestine of a suslik in a histamine solution at plus 50° brings about inhibition of the synthesis of acetylcholine and of its transfer out of the tissue. At plus 37° histamine sharply augments acetylcholine synthesis by the tissue of the suslik intestine, so that more acetylcholine is liberated into the surrounding solution.

- 5 -

S-E-C-R-E-T

S-E-C-R-E-T

50X1-HUM

The connection between the loss by smooth muscle tissue of sensitivity to histamine after cooling and the suppression of acetylcholine synthesis by histamine under the same conditions leads to the conclusion that histamine acts on the tissues in question by liberating acetylcholine. Histamine inhibits the synthesis of acetylcholine by nonirritated peripheral nerves (radix anterior and radix posterior of the spinal cord of a cat, the sciatic nerve, and the heart branch of the vagus) as well as by heart auricles. At the same time, liberation of acetylcholine from the tissue into the surrounding medium diminishes. In both irritated nerves and irritated auricles, histamine produces a sharp increase of acetylcholine synthesis and also of the liberation of acetylcholine from the tissue into the ambient liquid. In all cases the presence of acetylcholine in sensory nerves could be shown. Apparently histamine does not play an independent role in the process of nerve stimulation, but merely takes part in the chemical dynamics of metabolic processes that lead to the formation of acetylcholine.

"The Effect of Acetylcholine on the Activity of Amino Acid Decarboxylases,"
N. N. Demin, pp 115-124

Amino acids undergo the most diverse changes in the animal body. However, the principal manner in which they decompose is oxidative deamination under formation of alpha-ketoacids. In microorganisms, particularly microorganisms which produce putrefaction, intensive decarboxylation of amino acids occurs. This decarboxylation leads to the formation of carbon dioxide and of amines. The work of many investigators (both USSR and foreign) has shown that the tissue of various organs of mammals (kidneys, liver, pancreas, etc.) contains specific decarboxylases of l-amino acids. Notwithstanding the low activity of animal amino acid decarboxylases, they are of great interest because some products of the reaction catalyzed by them (histamine, tyramine, hydroxytyramine, tryptamine) may exert a strong physiological action even at very low concentrations.

The most noteworthy substance of this type is histidinedecarboxylase, because histamine forms as a result of its action. Histamine is contained in nerve tissue and its presence there must apparently have a specific functional significance. Thus, it is held that histamine plays a special role in sensory nerves which conduct impulses to the center (histaminergic nerves) and that it assists in bringing about the sensation of pain.

At the present time, data have been accumulated (particularly at the laboratory of Kh. S. Koshtoyants) which indicate that there is a definite relationship between histamine and acetylcholine, the chemical agent with the aid of which the functional activity of the parasympathetic and central nervous systems is brought about. In many cases, a certain parallelism between the contents of histamine and acetylcholine in nerves is observed (D. Ye. Ryvkina, *Byull Eksp Biol i Med*, Vol XXVI, p 349, 1948) and there are shifts in the concentrations of these substances when the functional condition of the nerve tissue is changed (D. Ye. Ryvkina, N. N. Bulatova, *Byull Eksp Biol i Med*, Vol XXII, No 3, p 32, 1946; D. Ye. Ryvkina, *Byull Eksp Biol i Med*, Vol XXIV, p 53, 1947). Frequently histamine and acetylcholine seem to exert a synergic effect. It appears very probable that histamine under certain conditions may act on tissues by bringing about the liberation of acetylcholine or by stimulating the synthesis of this substance.

Kh. S. Koshtoyants, D. Ye. Ryvkina, and R. L. Mitropolitanskaya (*DAN SSSR*, Vol I, p 390, 1945) established that in cases of traumatic injuries there is considerable activation of histidinedecarboxylase contained in nerve tissue. Furthermore, Ryvkina (1947) showed that irritation of peripheral nerves with an electric current of threshold strength also produces a rise in the activity

- 6 -

S-E-C-R-E-T

S-E-C-R-E-T

50X1-HUM

of histidinedecarboxylase. In the light of the experimental results obtained in this instance (see below), it appears plausible that intense trauma as applied by Koshtoyants (killing the animal by hitting it over the head) and electrical irritation (Ryvkina's method) result in the formation of acetylcholine. The acetylcholine in turn stimulates the activity of histidinedecarboxylase, thus leading to an increased formation of histamine.

The experiments performed in this instance show that the cerebrum of guinea pigs contains histidinedecarboxylase. Its activity is high enough to permit determination by the manometric method, i.e. by measuring the quantity of carbon dioxide which is evolved upon decarboxylation of L-histidine. Acetylcholine at concentrations of 1×10^{-8} - 1×10^{-4} (in the presence of physostigmine) may activate the histidinedecarboxylase contained in the brain of guinea pigs. In some cases acetylcholine does not exert any effect. If the concentration of acetylcholine is lower than 1×10^{-4} , its effect decreases. In the same range of concentrations, acetylcholine activates the histidinedecarboxylase of *Cl. Welchii* BW 21 without affecting argininedecarboxylase, glutamic acid decarboxylase, and lysinedecarboxylase which have been derived from other microorganisms. Apparently acetylcholine has the ability to activate bacterial aspartic acid decarboxylase to some extent.

The results indicate that acetylcholine may participate in the regulation of the content of histamine in nerve tissue by stimulating the formation of histamine.

"The Dependence of Galvanotaxis of Paramecia on the Metabolism and the Condition of Proteins," M. F. Popova, pp 125-143

"Participation of the Sympathetic Nervous System in the Awakening of Krapchaty Suslik (*Citellus suslica* Guehl) from Hibernation," T. M. Turpayev, R. S. Person, pp 144-147

During the awakening of susliks from hibernation, their blood contains considerable quantities of sympathicomimetic substances. The content of these substances drops after the animals have awakened. Isolated and perfused hearts of these animals react rapidly to adrenalin, but not to acetylcholine.

2. Material on Comparative Physiology of the Respiratory Function of the Blood of Vertebrate Animals.

"The Respiratory Function of the Blood of Porpoises," P. A. Korzhuyev, N. N. Bulatova, pp 151-164

Investigation of the blood of three species of Black Sea porpoises indicated that the concentration of hemoglobin in the erythrocytes of all three species is higher than in erythrocytes of land animals. This must be regarded as a form of adaptation to aquatic life.

"Erythrocytes and Hemoglobin of the Black Sea Pelamid (*Pelamys Sarda*)," N. N. Bulatova, P. A. Korzhuyev, pp 165-167

"The Content of Erythrocytes and of Hemoglobin in the Blood of Krapchaty Suslik During the Period of Hibernation," P. A. Korzhuyev, pp 168-172

"Binding of Carbon Dioxide by the Blood and the Acid-Base Balance in Krapchaty Suslik During Periods of Wakefulness and Hibernation," R. S. Person, pp 173-185

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- 7 -

S-E-C-R-E-T